Subject: FR Notice Comments - 76 FR 71977 - Update of the NICEATM-ICCVAM Five-Year Plan
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Comments: The American Chemistry Council (ACC) appreciates the opportunity to provide comments for consideration by the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the agency program offices of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) as the process gets underway to update the NICEATM-ICCVAM five-year plan to cover the period of 2013 through 2017 (http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/FR/FR-2011-30001.htm.)
The worldwide emergence of integrated testing strategies, tiered toxicity testing frameworks and decision triggers supports the view that toxicity and risk assessment has

clearly advanced from past use of rigid, ‘‘one size fits all’’ inflexible test batteries with a specific checklist of studies that are run in some defined sequence. Chemicals differ in many ways that influence toxicity and risk. Some substances such as pesticides and pharmaceuticals are designed to exert biological activities in certain organisms. In contrast, commodity chemicals and pesticide inert ingredients are not designed to exert biological activity and generally do not possess the same degree of biological activity as do pesticides or pharmaceuticals. Since risk is a function of inherent toxicity (influenced by chemical structure, physical, and chemical properties), susceptibility (which may be influenced by life stage), and exposure (influenced by dose, route, duration and activity patterns), production processes and use patterns that influence exposure will ultimately influence potential risks to human health. Therefore, there is a sound scientific basis for use of a testing strategy that is guided in part by how a chemical, such as a commodity substance, is used.

The evolution of toxicity testing methods toward the inclusion of in vitro and in silico approaches for hazard identification or screening has been based, in part, on the desire to reduce the use of animals in regulatory program-driven toxicity testing. These integrated testing strategies, which utilize relevant information from multiple sources, including predictive in silico models, chemical categories, in chemico, and in vitro assays are gaining greater acceptance as a way to provide estimates of toxicological properties in lieu of conducting actual animal toxicity tests. Integrated testing strategies (ITS) have been incorporated into the US HPV Challenge program, the OECD’s chemical evaluation program, the EU REACH legislation and the ICCA Global Product Strategy. Adequate characterization of these hazard profiling approaches is key to their practical application, this in turn implies an evaluation of their performance attributes including relevance, reliability, sensitivity, and specificity. Moreover uptake and confidence in these approaches will be reliant on how the different elements are integrated both qualitatively and to a larger extent quantitatively; the latter could make use of decision analysis techniques. Characterizing ITS in this systematic way will make assumptions explicit, thus regulatory agencies, the regulated community, and the public will be better informed of the scope and limitations of ITS

approaches and should in turn have greater confidence in relying on the use of this knowledge for decision making that is protective of health and the environment. As such, the ICCVAM-NICEATM 5-year plan should consider how decision analysis techniques incorporating value of information (VOI) analysis for example, could be effectively utilized to guide risk assessors towards the optimum combination of testing/information, whether it be in vitro, in vivo, or in silico. A VOI approach estimates the value of reducing the uncertainty in the key factors affecting a decision, thus any testing to be conducted is targeted in its design. This approach serves to identify the most relevant testing strategy rather than just presuming a standard animal toxicity test battery is the best way of addressing the information requirements of a risk assessment.

The potential application of such tools as ToxCast and Tox21 can range from priority setting to use as surrogate information in lieu of traditional animal toxicity tests within an integrated testing and assessment framework. However, for each and every proposed application, these tools must first be characterized in terms of their performance, applicability domain and mechanistic relevance. i.e., where the tools fit in the context of a Mode of Action (MOA) or Adverse Outcome Pathway (AOP) framework. If tools are not appropriately characterized prior to being used for screening/prioritization it will convey a false sense that those screening decisions are based on data that have a demonstrated ability to predict downstream events of concern for human health. Once a tool/method is appropriately characterized in terms of its performance and biological context, then an informed decision can be made whether the level of uncertainty associated with the results of a particular tool/suite of tools is sufficient for its intended use. In the revision of the 5-year plan, ICCVAM-NICEATM should consider the role of ICCVAM in demonstrating that these methods and tools are scientifically valid for their intended purpose before they are deployed for regulatory use across numerous agencies. ICCVAM-NICEATM should also ensure that there are several open forums over the 5-years to allow public / stakeholder comments to be heard and considered. In addition, ICCVAM-NICEATM should also consider closer collaboration with other agencies and partner organizations (e.g. ECVAM, JACVAM) to avoid any

duplication of efforts in moving towards a Tox21 vision and to ensure that tools and approaches are harmonized and hence potentially applicable across other regions.
As noted, there are several activities and projects around the globe that are focused on developing the best methods for incorporating these new in vitro and in silico technologies into tiered-testing and risk assessment practices. The participants in these projects span the stakeholder spectrum and no single stakeholder has all of the answers. Therefore, it will take a mutual effort from all stakeholders to develop the best and most reliable frameworks and methods for incorporating Tox21 methods in to toxicity testing and risk assessment. ICCVAM-NICEATM should plan for multi-stakeholder involvement in these activities and projects.
